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10/541,277	06/08/2006	Friedhelm Brassel	13455/1	6606

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EXAMINER	
ARNOLD, ERNST V	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/541,277	BRASSEL, FRIEDHELM	
	Examiner	Art Unit	
	ERNST V. ARNOLD	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 April 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-19 and 21-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-19 and 21-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-16 and 20 have been cancelled. Claims 17-19 and 21-29 are pending and under examination. Applicant's amendments have necessitated a new ground of rejection. Accordingly, this Action is FINAL.

Withdrawn rejections:

Applicant's amendments and arguments filed 12/23/09 and 4/12/10 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed below is herein withdrawn. Claims 17-29 were rejected under 35 U.S.C. 103(a) as being unpatentable over Rump et al. (Eur J Clin Pharmacol 2002, 58, 459-465) in view of Doerfler et al. (Neuroradiology 2001, 43, 1112-1117). Applicant has amended the claims to overcome this rejection. Accordingly it is properly withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 17-19 and 21-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Doerfler et al. (Neuroradiology 2001, 43, 1112-1117) and Dubois et al. (Pediatr Radiol 2003, 33, 365-372; PTO-892 filed on 5/16/08) and Rump et al. (Eur J Clin Pharmacol 2002, 58, 459-465).

Applicant claims

17. (Currently Amended) A medical kit for use in a method to produce a liquid embolizate ready for use in a method for treatment vascular malformations, said liquid embolizate ~~comprising~~ consisting of:

(a) ~~20 to 80%~~ 30 to 70 % v/v of an occlusion mixture containing a zein emulsion in aqueous ethanol,

(b) ~~10 to 40%~~ 15 to 35 % v/v of a radiopaque contrast medium in liquid form and

(c) ~~10 to 40%~~ 15 to 35 % v/v of ethanol,

the percentages of components (a), (b) and (c) adding up to 100% of the liquid embolizate, components (a), (b) and (c) being separately packed and drawn-up into syringes,

the kit further including at least one empty syringe for accommodation of the readily prepared liquid embolizate and a three-way cock.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Doerfler et al. teaches Ethibloc (60% ethanolic zein) and Lipiodol compositions in ratios of E/L 1:1, 1:2 and 1:3) (Abstract and page 1113, table 1 and Ethibloc right column). Doerfler et al. teach injection through a microcatheter is not smooth because of Ethibloc's high viscosity and to decrease the viscosity by mixing with the oily contrast medium Lipiodol (page 1113, right column Ethibloc). From page 1113:

> **Ethibloc (Ethicon, Norderstedt, Germany) is an ethanolic (60%) solution of 210 mg zein (corn protein)/ml ethanol, 162 mg sodium amidotrizoate/ml ethanol, 145 mg oleum papaveris/ml ethanol and 6 mg propyleneglycol/ml ethanol. As the alcohol dissolves in aqueous media, zein precipitates and forms a cast with a consistency resembling "chewing gum".**
>
> **Injection through a microcatheter is not smooth, because of Ethibloc's high viscosity. To decrease this high viscosity and to enhance visibility under fluoroscopy, Ethibloc can be mixed with the iodinated contrast agent Lipiodol in different solutions.**

Oleum papaveris is another term for poppy seed oil. Amidotrizoate is a radiopaque agent. Methods of mixing Ethibloc in 3-way tap with Lipiodol with 1 cc syringes are taught (page 1113, study design). Doerfler et al. teach that the high viscosity of Ethibloc can become a problem with certain microcatheters which rupture while the embolic agent is injected (page 1115, lower right paragraph through page 1116). Doerfler et al. teach embolization of arteriovenous malformations (Introduction, page 1112), which reads on at least arteriovenous short circuits/vascular malformations and cerebral malformations as well as capillary embolization of the kidneys (page 1113, left column). Furthermore, Doerfler et al. teach using a guidewire-directed microcatheter with Ethibloc (page 1116).

Doerfler et al. establish that: 1) Ethibloc is highly viscous and problematic for injection and 2) Lipiodol is a known contrast medium in liquid form that can be used to dilute Ethibloc.

Rump et al. teach sealing the hepatic artery by injection of 0.2-0.5 ml Ethibloc emulsion consisting of (8 ml Ethibloc, 1.5 ml Lipiodol, and 1.5 ml ethanol) (Page 461, left column second paragraph). The total volume would be 8 + 1.5 + 1.5 = 11 ml. thus the v/v% would be about:

Ethibloc = 8/11 X 100% = 72.7%

Lipiodol = 1.5/11 X 100% = 13.6%

Ethanol = 1.5/11 X 100% = 13.6%

Thus, the Rump eta l. establish the concept of diluting ethibloc with both lipiodol and ethanol. The volume ratio of lipiodol to ethanol is 1:1 which is between 1:2 and 2:1.

Dubois et al. teach diluting 7.5 ml Ethibloc with 5 ml 100% ethanol (page 368, lower left column) which results in 12.5 ml solution consisting of 60% Ethibloc and 40% ethanol. ***Dubois et al. establish diluting Ethibloc with ethanol.***

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

1. The difference between the instant application and Doerfler et al. is that Doerfler et al. do not expressly teach a liquid embolisate that consists of 30 to 70% v/v of component (a) and 15 to 35% v/v each of components (b) and (c) in a medical kit comprising components (a), (b), and (c) being separately packed and drawn up into syringes and at least one empty syringe for accommodation of the liquid embolizate and a 3-way cock. This deficiency in Doerfler et al. is cured by the teachings of Rump et al. and Dubois et al.

2. The difference between the instant application and Doerfler et al. is that Doerfler et al. do not expressly teach a wherein the mixing takes place under vacuum or the elimination of air is achieved by centrifuging. This deficiency in Doerfler et al. is cured by common sense of the ordinary artisan.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to make a liquid embolisate that consists of 30 to 70% v/v of component (a) and 15 to 35% v/v each of components (b) and (c) in medical kit with components (a), (b), and (c) being separately packed and drawn up into syringes and at least one empty syringe for accommodation of the liquid embolizate and a 3-way cock and , and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because: 1) Doerfler et al. teach that even after dilution of Ethibloc with lipiodol the composition can still rupture the catheter thus motivating one of ordinary skill in the art to look to means to further dilute the composition to decrease the viscosity and since the art suggests diluting Ethibloc with both ethanol and lipiodol and it is just routine optimization of the amounts taught in the art to arrive at the instant claimed ratio; 2) each of the solutions has to be stored somewhere and Doerfler et al. teach methods of mixing Ethibloc in 3-way tap, which would constitute a 'mixing system', with Lipiodol using syringes (page 1113, study design) which provides an easy and convenient means to store the solutions, quickly mix the solutions for use, and to use the empty syringe to hold the

mixed solution just before injection. The art already teaches Ethibloc solutions with 13.6% ethanol (Rump) and up to 40% ethanol (Dubois). Any amount of ethanol in between is obvious to the ordinary artisan and it simply because merely routine optimization. Therefore, in the absence of evidence to the contrary, storage of the components in 3 separate syringes and having a fourth syringe for injecting the mixed solution would be obvious to one of ordinary skill in the art.

2. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use the method of Doefler et al. wherein the mixing takes place under vacuum or the elimination of air is achieved by centrifuging and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because, absent unexpected results, it is merely a design choice by the artisan to remove air from the embolic which is obvious to do before injection into a patient.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to arguments:

While Applicant's arguments are moot in view of the new ground of rejection, the Examiner will address the Declaration filed on 2/24/10. The Declaration would still be

insufficient to overcome the instant rejection because it is a declaration without objective evidence for the Examiner's consideration. For example, the assertion in paragraph 7 that rapid separation of the oily contrast medium from the genuine ethibloc during embolization is without objective data. Also in paragraph 7 is the assertion that the alcohol in Doerfler et al. was warmed leading to vaporization of the alcohol out of the genuine ethibloc changing the emulsion to an unstable suspension. Again, nothing has been shown to substantiate this and the section of Doerfler et al. to support this statement was note cited. Applicant asserts in paragraph 9 that catheters of 1.2 French can be used but nothing has been shown that, for example, the composition of Rump et al. would not work in such a catheter as it is reasonable to assert that since the composition are so close in the amounts of ingredients that a similar function would be obtained. In paragraph 10, it is asserted that a wider window time is obtained but nothing has been shown for comparative analysis. From MPEP 716.01(c) II: The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965).

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness. Respectfully, the claims remains rejected at this time.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ernst V. Arnold whose telephone number is 571-272-8509. The examiner can normally be reached on M-F (7:15 am-4:45 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Ernst V Arnold/
Examiner, Art Unit 1616